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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/727,236	11/30/2000	Russell J. Linderman	5051.509	4373

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	12

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/727,236	LINDERMAN ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *15-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 11 (filed 6/14/02), claim 1 has been amended. Claims 1-60 remain pending; claims 15-60 remain withrawn from consideration.

Applicants' arguments filed 6/14/02 have been considered and found persuasive in part.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As indicated previously, applicants have proposed that the compounds (to which the claims are drawn) inhibit insect propagation by a process in which esterase biosynthesis is inhibited by a process which begins with stimulation of the TMOF receptor. However, there is no evidence that the TMOF receptor is affected one way or another by the compounds, or that esterase biosynthesis is affected one way or another by the compounds. In addition, it remains unknown at this time whether insect propagation is in any way altered.

In response to the foregoing, applicants have essentially argued that if a rejection under

35 USC §101 has not been imposed, or if such a rejection should not be imposed, then in that situation, a rejection under 35 USC §112, first paragraph (lack of enablement) is necessarily improper. However, applicants are not correct. While it may be true that a rejection under 35 USC §101 is frequently accompanied by a rejection under 35 USC §112, first paragraph, that fact that a rejection under 35 USC §101 has not been imposed in a given application has no bearing whatsoever on the validity of a rejection under 35 USC §112, first paragraph. In the instant case, it is true that no rejection has been imposed under 35 USC §101. Accordingly, the issue of "utility" need not be discussed further.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As it happens, in the pursuit of insecticides, structure/activity relationships are unpredictable, and many insects are resistant.

- The following references disclose that insects develop resistance. Some of the references disclose that increased esterase activity is one of the mechanisms:

  Lee, Sung-Eun (*Agricultural Chemistry and Biotechnology* **44**(3), 105-112, 2001)

  Field, L. M. [Biochemical Sites of Insecticide Action and Resistance (2001), 209-219. Editor(s): Ishaaya, Isaac. Publisher: Springer-Verlag, Berlin, Germany]

Devorshak, Christina (*Reviews in Toxicology (Amsterdam)* 2(7,8), 501-537, 1998)

Wilkins, R. M. (*Brighton Crop Protection Conference--Pests and Diseases* (vol. 2), 511-516, 1998)

Feyereisen, R. (*Toxicol. Lett.* (1995), 82/83(1-6), 83-90, 1995)

In addition to the foregoing, the following references disclose either(a) that compounds may be highly effective against some insects, but not others, or (b) that minor structural changes can eliminate activity:

- Inoue (USP 4752417) discloses (col 1, line 19+) that a change at one chiral center can eliminate insecticidal activity.
- Wolfe(USP 4,342,176) discloses (col 2, line 58) that a given insecticide may be highly active against one insect species and inactive against another.
- Stehrer-Schmid, Paula (*Mutation Research* **339**(1), 61-72, 1995) discloses that three 2,3-dihydro-2,2- dimethylbenzofuran derivs. without a carbamate function are inactive.
- Kay, I. R. (*Crop Prot.* **12**(4), 310-14, 1993) discloses that Diazinon, carbofuran and dimethoate were ineffective against the eggfruit caterpillar (*Sceliodes cordalis*).
- Yamauchi, Satoshi (*Biosci., Biotechnol., Biochem.* **56**(11), 1760-8, 1992) discloses that the 3,4-dimethoxyphenyl analog was totally inactive, even at a high dose level.
- VanWagenen, Bradford C. (*J. Org. Chem.* **58**(2), 335-7, 1993) discloses that a structurally related compound, di-Me N2-creatininylphosphate (II), was inactive in the insecticidal screens.
- Yoshikawa, Hiromichi (*Biosci., Biotechnol., Biochem.* **56**(9), 1467-9, 1992) discloses that the 6-nitro derivs. were completely inactive as insecticides.

- Kole, Ramen K. (*J. Agric. Food Chem.* **40**(7), 1208-10, 1992) discloses that rotenone was very active, but dehydrorotenone was found to be completely inactive

- Dhingra, Swaran (*J. Entomol. Res.* **14**(2), 139-41, 1990) discloses that lindane and malathion were ineffective against the mealy bug.

- Mitsudera, Hiroyuki (*Nippon Noyaku Gakkaishi* **16**(3), 387-95, 1991) discloses analogs of nereistoxin that are insecticides. Also disclosed is that minor structural changes eliminated activity.

- Carmellino, M. L. (*Boll. Chim. Farm.* **129**(5), 190-4, 1990) discloses insecticidal activity of quinolinecarboxylic acids, as well as minor structural variants that are inactive.

In addition, applicants have proposed that the compounds may act by stimulating the TMPOF receptor. Each of the following references discuss the issue of receptor activation (or receptor antagonism) versus *in vivo* activity. As it happens, the relationship between the two is "unpredictable":

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, and discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.

- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]NH_2 (Et): effects on opioid receptor binding and activation" (*Journal of Peptide Research* (2000 Mar) 55 (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.

- Keith , "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects

of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.

- Xiao (*Biochemistry* **40**, 2860, 2001) has looked at the relationship between cAMP production in cells, and *in vivo* activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional determinantants of *in vivo* activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased *in vivo* insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an increase in *in vivo* insulinotropic activity. Thus, receptor activation is not necessarily predictive of *in vivo* activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) 2 (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [125I]-Nle4-D-Phe7-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity.

Accordingly, "undue experimentation" would be required to determine which, if any, of the claimed compounds can be used to inhibit esterase biosynthesis or to inhibit propagation of insects.

*

Claims 1-14 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for

failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Many of the dependent claims (e.g., claim 2) recite the phrase "said pest". This term now lacks antecedent basis.

- Claim 1 is indefinite as to the process steps and endpoint. In the event that applicants have shown that the compounds inhibit biosynthesis of a serine esterase, it is suggested that the claims be amended to recite that the time and conditions are indeed effective to accomplish this objective, i.e:

  100. A method for inhibiting propagation of insects comprising administering to said insects a compound of formual IA or formula IB
  {formulas as recited}
  for a time and under conditions effective to inhibit biosynthesis of a serine esterase... [etc.]

  On the other hand, if applicants have shown that the compounds stimulate the TMOF receptor, it is suggested that the claims be amended to recite that the time and conditions are indeed effective to accomplish this objective, i.e:

  101. A method for inhibiting propagation of a insects comprising administering to said insects a compound of formual IA or formula IB
  {formulas as recited}
  for a time and under conditions effective to stimulate the trypsin modulating oostatic factor (TMOF) receptor...[etc.]

  If applicants have shown that the compounds do indeed reduce the rate of reproduction of certain insects, then other claim language may be appropriate.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton. Phone: (703) 308-3213.

An inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800